INVITED REVIEW

The US Food and Drug Administration investigational device exemptions (IDE) and clinical investigation of cardiovascular devices: Information for the investigator

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The conduct of a clinical investigation of a medical device to determine the safety and effectiveness of the device is covered by the investigational device exemptions (IDE) regulation. The purpose of IDE regulation is "to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of useful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose" (Federal Food, Drug, and Cosmetic Act). Conducting a clinical investigation may require an approved IDE application. The US Food and Drug Administration encourages early interaction with the agency through the pre–IDE process during the development of a device or technology and during the preparation of an IDE application. This facilitates approval of the IDE application and progression into the clinical investigation. This paper reviews the terminology and applicability of the IDE regulation and the type of study that requires an IDE application to the Food and Drug Administration. The pre–IDE process and the development of an IDE application for a significant risk study of a cardiovascular device are discussed. (J Vasc Surg 1999;29:566-74.)

The US Food and Drug Administration (FDA) is charged by Congress under the Federal Food, Drug and Cosmetic Act with the responsibility of regulating medical devices to assure their safety and effectiveness. Under this law, medical devices intended for human use are subject to a variety of controls and must be properly labeled and packaged, be cleared for marketing by the FDA, meet their labeling claims, and be manufactured in accordance with good manufacturing practices. When Congress established the FDA's current authority in device regulation in 1976, it recognized that the discovery and development of new devices would require exemption from many of these requirements that apply to devices in commercial distribution. Accordingly, Congress authorized the FDA to exempt investigational devices from certain requirements of the Federal Food, Drug and Cosmetic Act. This legal authority and the investigational device exemptions (IDE) regulation that implements it are intended "to encourage, to the extent consistent with the protection of public health and safety and with ethical standards, the discovery and development of use-

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ful devices intended for human use, and to that end to maintain optimum freedom for scientific investigators in their pursuit of this purpose."[1,2]

Conducting a clinical investigation of a medical device requires approval under the IDE regulation before the study begins, with the exception of some studies that are specified in the regulation.[3] An *investigation* is a clinical investigation or research, which involves one or more subjects, to determine the safety or effectiveness of a device. A clinical study is exempt from the IDE regulation if the device is used or investigated in accordance with the indications in the approved labeling. For example, a comparative study of two endovascular stents for implantation in the common iliac artery for the treatment of stenosis as a result of atherosclerotic disease in which both devices are approved for that indication would not require the submission of an IDE application. The local institutional review board (IRB) may require approval of the study at its discretion. In contrast, if a study is designed to compare two stents for the creation of an intrahepatic portosystemic shunt for prophylaxis of variceal bleeding and one stent is approved for that indication and the other is not, then an IDE application would be required. Both FDA and IRB approval would be required before the initiation of the study.

The degree of risk involved in the study determines the level of regulatory control required. A nonsignificant risk study may be approved by the local IRB. A significant risk study, that is, one which "presents a potential for serious risk to the health, safety or welfare of a subject,"[4] requires approval of an IDE application by the FDA and may not be conducted without the approval of both the IRB and the FDA. In either case, the IDE regulation provides for the procedures for the conduct of clinical investigations of devices, including informed consent for all patients, adequate patient and data monitoring, and maintenance of necessary records and reports. The investigations must meet the regulatory requirements regarding ethical conduct of human studies, requirements which adhere to the ethical guidelines of the World Medical Association Declaration of Helsinki on the protection of human subjects in biomedical research.

This paper discusses the pre–IDE process and the content of IDE applications to the FDA for the approval of studies that pose a significant risk. An overview of the regulation of medical devices by the FDA has recently been presented elsewhere.[5]

FDA REVIEW OF IDE APPLICATIONS

Within the FDA, the regulation of devices is the responsibility of the Center for Devices and Radiological Health. Within the center, the evaluation of applications for approval of clinical investigations, commercial marketing, and labeling of cardiovascular devices is performed by the Division of Cardiovascular, Respiratory and Neurological Devices in the Office of Device Evaluation. The review team for an IDE application may include medical professionals, scientists, engineers and biostatisticians, as appropriate for each application. In addition, there are two committees within the division that serve as resources for the review teams: the Pre-Clinical Trials Board and the Clinical Trials Board. The Pre-Clinical Trials Board is composed of pathologists, physiologists, and biomedical engineers and provides guidance on animal testing. The Clinical Trials Board reviews clinical research protocols submitted to the division. The members of the board are medical officers and other persons on the staff of the center with experience in the review of investigational protocols for cardiovascular devices, such as senior reviewers and biostatisticians. The meetings provide a forum for the discussion of the application among the primary reviewers and the members of the board who may not be directly involved in the review of the application. The medical specialties currently represented on the board are anesthesiology, cardiology, cardiovascular and thoracic surgery, nuclear medicine, pathology, and radiology.

The FDA is also assisted in its review of device applications by a system of external experts who review critical issues and serve in an advisory role. This Medical Devices Advisory Committee is composed of experts in a broad range of medical specialties. The committee is subdivided into 16 panels according to clinical area and device specialty, such as the Circulatory System Devices Panel. The primary role of the panel is the review of certain marketing applications, but it may also provide advice on device classification, potential risks, development of study protocols, and the content of guidelines or guidance documents. The advisory panels provide the FDA with scientific and medical expertise from the user community, which helps to ensure that the decision-making of the FDA reflects the state-of-the-art in medical practice and technology. In addition, the FDA benefits from its interactions with professional societies, the medical community, and device manufacturers, and from the discussion of issues of mutual concern.

PRACTICE OF MEDICINE VERSUS CLINICAL INVESTIGATION

Historically, the FDA has purposefully avoided regulating the practice of medicine and has taken the

Table I. Pertinent regulations

Investigational device exemptions	21 CFR Sect 812.
Protection of human subjects	21 CFR Sect 50.
Institutional review boards	21 CFR Sect 56.

position that physicians must have the latitude to do whatever is in the best interests of their patients.[6] The FDA's articulated policy states that "good medical practice and patient interests require that physicians be free to use commercially available drugs, devices and biologics according to their best knowledge and judgment. If a physician uses a product for an indication not in the approved labeling, he or she has the responsibility to be well informed about the product and to base its use on a firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects."[7] Use of a legally marketed device for an "off-label" indication as part of the practice of medicine does not require clearance through the FDA but may require review by an IRB, depending on the individual IRB requirements.

In contrast, research that involves one or more subjects to determine the safety or effectiveness of a device is not within the realm of the practice of medicine, whether or not the device is legally marketed. These clinical investigations must be conducted in accordance with the IDE regulation. For example, because the safety and effectiveness of endovascular grafts have not been shown, these devices should only be used as part of a clinical investigation. Specific questions as to whether a particular use of a device is considered practice of medicine or is a clinical investigation may be directed to the physician's IRB or the FDA.

SIGNIFICANT RISK STUDY VERSUS NONSIGNIFICANT RISK STUDY

If the use of a device is investigational, then the distinction must be made as to whether the study constitutes a significant risk study or a nonsignificant risk study. This decision is crucial because it determines the level of regulatory control to which the study will be subject.[8,9] A *significant risk study* is defined by the IDE regulation as one which "presents a potential for serious risk to the health, safety, or welfare of a subject."[4] The determination of significant risk is on the basis of the nature of harm that may result from the use of the device in the investigation, including the potential harm that could be caused by any procedure used in conjunction with the device. It is the risk of the study, not the device, that is the issue. For example, if a device is implanted as part of a surgical procedure, the potential for harm from the surgery is considered in determining whether the study constitutes a significant risk. In addition, the risk should be determined on the basis of absolute risks, not risk relative to an existing device. For example, it would be inappropriate to categorize a study of a covered stent as a nonsignificant risk study on the basis of the common usage of bare stents or the perceived advantages over current stents. The absolute risk—that failure could be life-threatening or injurious—dictates that it is a significant risk study.

The local IRB makes the determination as to whether a study is a significant risk or nonsignificant risk study. However, the FDA retains the final authority to make that determination. If a study is a nonsignificant risk study, then the IRB acts as an FDA surrogate and may approve the study without direct FDA involvement.[10] If a study constitutes a significant risk, the sponsor must explicitly apply to the FDA for approval of an IDE application. The study may not proceed unless both the FDA and the IRB approve the IDE application, but the sponsor need not wait for IRB approval before submitting the IDE application to the FDA, nor vice versa. As an example, vascular stents and vascular graft prostheses are considered significant risk devices as a result of the inherent risks that are associated with the use of these devices. Both FDA and IRB approval would be required before the initiation of a study that involved these devices.

OVERVIEW OF THE PRE–IDE PROCESS AND IDE APPLICATIONS

Once a determination is made that a study is a significant risk study, an IDE application must be submitted to the FDA and approved or conditionally approved before the clinical study may begin. The Investigational Device Exemptions Manual reviews the regulatory requirements, discusses practical issues related to the submission of an IDE application, and contains other useful documents from the FDA, including copies of the pertinent regulations (Table I). A listing of sources of information is included in Table II. The IDE application may be submitted by the manufacturer of a device for the collection of data to support a future marketing application or by a responsible investigator who wishes to conduct an investigation of the safety and effectiveness of a device. Early and continued interactions between the sponsor and the FDA through the pre–IDE process is encouraged to expedite the development of an IDE application.

The pre-IDE interactions between the sponsor and the FDA occur during the sponsor's development of a device and the clinical research protocol. Product development is a dynamic process, and interactions with the FDA may be initiated at any stage of the developmental process. Communication with the FDA through a pre-IDE application before the formal submission of an IDE application helps to identify the issues and concerns that will need to be addressed in the IDE application and facilitates approval of the IDE application. These early informal interactions may be implemented through teleconferences, personal meetings, or written submissions and are considered strictly confidential as are formal IDE applications. The extent of pre-IDE interactions will depend on the complexity and novelty of the device and the related issues and, to some extent, on the experience of the sponsor in preparing IDE applications. Early interaction during the development process will help to make clear to the sponsor what the FDA's expectations will be for the content of a particular IDE application.

In the formal IDE application, the proposed investigational plan must be adequately justified on the basis of the report of prior investigations included in the application (ie, all prior laboratory, animal, and clinical testing of the device). In addition, the application must establish the following: (1) the rights, safety, and welfare of study subjects will be protected; (2) the anticipated benefits or the importance of the knowledge to be gained outweigh the risks to the research subjects; (3) the investigation is scientifically sound with the expectation that useful data will be gathered in the study; (4) the distribution of the investigational devices will be controlled; and (5) adequate records and reports will be maintained. In evaluating an IDE application, the FDA understands that not all can be known about the device before the study. However, safety issues are to be addressed by the bench and preclinical testing before human use testing, and due care in the device design, investigational planning, and protection of human subjects, including adequate informed consent from the study subjects, is required.

In preparing a clinical protocol, one should consider a feasibility study involving a small number of study subjects as the first step.[11] The purpose of these studies is to initiate investigator experience, establish an operator learning curve, assess design adequacy, address specific safety issues, further define the clinical protocol, and evaluate the potential efficacy of the device. The feasibility study may be subsequently expanded to a full study by submission of an IDE supplement.

Once an IDE application has been filed, the FDA has 30 days in which to make a determination of whether to approve, conditionally approve, or disapprove the application. That decision is made on the basis of the adequacy of the device description, the report of prior investigations, the investigational plan, and compliance with the applicable portions of the IDE regulation. The clinical investigation may be initiated once the study has been approved by both the FDA and the local IRB.

An application that receives conditional approval requires, within 45 days, the submission of a supplement that contains the information requested in the conditional approval letter. The clinical investigation may be initiated once the FDA has issued a conditional approval decision and need not wait for full approval, provided that the IRB has also approved the study. If the conditions of approval are not met within the 45-day period, the FDA may propose discontinuation of the study.

If the FDA disapproves the application, the letter to the sponsor will delineate the deficiencies and identify the information necessary to correct the application. The sponsor then may submit an amendment to the IDE application that addresses each deficiency.

After approval, there are a number of required communications with the FDA. For example, supplements are submitted for the addition of new institutions or facilities, for changes in the investigational plan or device, and for reports on the progress of the study. The intent of these communications is to assure the continued protection of the study subjects and to maximize the sharing of vital information as the study progresses.

THE PRE–IDE PROCESS

The purpose of the pre–IDE process is to proactively identify and address issues and concerns regarding the development, evaluation, and performance of an investigational device. This process is intentionally flexible and may be adapted to meet the needs of the individual sponsor. The following discussion illustrates the types of data and information that may be presented in a pre-IDE application or during a pre-IDE meeting with the FDA, depending on the stage of development of the device at the time of the meeting. The discussion also reflects the types of questions that the FDA may have regarding a device and the types of information that may be needed to adequately evaluate the scientific justification of the formal IDE application. This information ahould serve as a guide for the

preparation, general approach, and motivation for early contact with the FDA.

The pre–IDE process is particularly useful in developing the report of prior investigations. Voluntary standards and FDA guidance documents may be helpful in developing this section. However, for innovative technologies, it is not only necessary to list the tests to be conducted but also to show that the testing plan is appropriate and comprehensive. One method to identify appropriate testing is to define the device and its intended use, evaluate the potential failure modes and clinical complications, and determine the testing needed to address each identified issue. Once the testing strategy is defined, the appropriate test methodologies may be developed, including bench, animal, and human studies.

The basic information clearly defines the device and its intended use. The device description includes a physical description of the device, including all the accessories, such as delivery catheters and adjunctive equipment, and a description of any modifications made to currently marketed devices used with or as part of the device. The information should include the following descriptions: what the device is intended to do and under what conditions or environments; how it does what it is intended to do; how long it should be able to do what it is intended to do; and for what patient population it is intended. Literature support should be provided where appropriate.

This basic information then can be used to identify the appropriate types of tests that should be conducted, and it serves as a foundation for the development of a testing strategy for the device. In developing the test plan, the potential safety and effectiveness issues are identified through an analysis of the potential failure modes of the device, and a list of tests that address each issue is complied. In addition, tests are developed that are designed to characterize the device and show conformance to design specifications. The section should include a discussion of the device design and review process and the design analysis, design implementation, and verification or validation processes.

Once the appropriate tests have been identified, the test methodologies can be developed on the basis of the intended use of the device and the anticipated safety and effectiveness issues. The rationale and justifications of the test methodologies should be on the basis of statistical or clinical rationale or both, with literature support when appropriate. The testing may include preclinical in vitro, preclinical in vivo, and clinical investigations. In general, each test method should state the purpose of the test with a clear statement of the hypothesis to be tested and should identify the safety and effectiveness issue that it is intended to address and the relevant parameters and variables to be assessed. The test description should show how the study design answers the question posed.

Once sufficient preclinical data are collected, the report of prior investigations may be finalized. The report of prior investigations should follow the logical progression of device development and testing and should include reports of all prior laboratory and animal testing of the device and any prior clinical experience with the device. It should be comprehensive and should provide adequate information to show the acceptability of the results obtained to justify the proposed clinical investigation. There also must be an indication as to whether nonclinical studies were performed in compliance with applicable requirements in the good laboratory practice regulations. The report also must include the following: a bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety or effectiveness of the device; copies of all published and unpublished adverse information; copies of other significant publications if requested by an IRB or FDA; and a summary of all other unpublished information (whether adverse or supportive) that is relevant to an evaluation of the safety or effectiveness of the device.[12]

The investigational plan may be finalized as the report of prior investigations is completed. The requirements for the investigational plan are delineated in the IDE regulation and should be presented in detail, including the purpose, research protocol, risk analysis, description of the device, and consent materials. As listed in the regulation, the purpose states the intended use of the device and the objectives and duration of the investigation. The written protocol describes the methodology to be used and an analysis of the protocol showing that the investigation is scientifically sound. The risk analysis includes a description and analysis of all the increased risks to which the subjects will be exposed by the investigation, the manner in which these risks will be minimized, a justification for the investigation, and a description of the patient population, including the number, age, sex, and condition of the subjects. Copies of all forms and informational materials to be provided to the subjects to obtain their informed consent should be included.[13]

THE IDE APPLICATION

Once adequate information is available to justify the initiation of a clinical investigation, an IDE appli-

cation may be submitted to the FDA for approval of a human study of the device. The application may be for a feasibility study[11] or for a larger and more comprehensive investigation. The requirements for the content of the application are delineated in the IDE regulation.[14]

The IDE Manual contains a copy of the administrative checklist used by the reviewers. By observing the requirements, one may prepare a complete application for submission to the FDA. The FDA review of the application is not merely a review of the checklist but also considers the device description, the intended patient population, alternative procedures or courses of treatment, associated risks and benefits and their magnitudes, whether useful data will be collected from the study as planned, whether the device is a relatively new technology or a modification to an existing device, and whether the investigation is scientifically sound.

A time line that projects the completion of the bench or animal testing should also be included because the degree of completeness of the bench or animal testing required for approval of an IDE application depends on the details of the application being submitted. For example, the requirements may be less strict for the initiation of a small feasibility study with the understanding that a higher level of completion will be required for expansion to a larger or more definitive study. For a device intended for commercial marketing, additional testing may need to be completed before the time the marketing application is submitted to the FDA. In that case, the application should identify the information that will be collected for the expected marketing application.

REIMBURSEMENT BY THE HEALTH CARE FINANCING ADMINISTRATION

The Health Care Financing Administration (HCFA) does not provide coverage for experimental devices but may provide reimbursement for nonexperimental investigational devices provided that the device is used in accordance with the IDE regulation. The HCFA recognizes that there are devices that are refinements or replications of existing technologies. Although an approved IDE application may be required for studies of the safety and effectiveness of a particular device, there may be scientific evidence that similar devices can be safe and effective. If the FDA has determined that the device type can be safe and effective, the devices will be considered for possible coverage. For example, the HCFA will consider for possible coverage those investigational devices that are of the same type as a device for which a manufacturer has received FDA clearance or approval for marketing.

To assist the HCFA in its coverage decisions, the FDA assigns each device with an approved IDE application to one of two categories: experimental/investigational devices (category A) or nonexperimental/investigational devices (category B). The *category A device* is an innovative device for which "absolute risk" of the device type has not been established—that is, initial questions of safety and effectiveness have not been resolved and the FDA is unsure whether the device type can be safe and effective. Category A devices are excluded from Medicare coverage. The *category B device* is a device for which the incremental risk is the primary risk in question—that is, underlying questions of safety and effectiveness of that device type have been resolved—or it is known that the device type can be safe and effective because, for example, other manufacturers have obtained FDA approval for that device type. The HCFA will consider coverage of a category B device for Medicare beneficiaries who participate in an approved clinical investigation. The intention is to provide Medicare beneficiaries with greater access to advances in medical technology and to encourage clinical researchers to conduct high-quality studies of newer technologies. As a general rule for all medical care, the HCFA has the authority to conduct a separate assessment of the appropriateness of an item or a service for Medicare coverage, including whether it is reasonable and necessary specifically for its intended use for Medicare beneficiaries.[15,16]

DILEMMAS IN THE REGULATION OF NEW TECHNOLOGIES

The introduction of new technologies also presents new clinical and regulatory concerns that must be addressed. These may relate to the risk-benefit analysis, the safety and effectiveness of the device, or the clinical evaluation and management of patients. The introduction of endovascular grafts for the treatment of abdominal aortic aneurysms provides a number of examples. The balance of risks and benefits for endovascular grafts differs from that for the alternative therapy—open surgical repair. Placement of endovascular grafts may have a lower perioperative morbidity and mortality rate as compared with open surgical repair, but the endovascular grafts may not be as effective because they have the potential for the incomplete exclusion of an aneurysm. There are new safety considerations, such as the potential for device migration or strut fracture. There are also

Table II. Sources of information from the Food and Drug Adminstration

Center for Devices and Radiological Health web site: http://www.fda.gov/cdrh/
Investigational Device Exemptions Manual (HHS Publication FDA 96-4159): http://www.fda.gov/cdrh/manual/idemanul.html or WordPerfect 6.1 file on a 3.5-inch floppy disk from the Division of Small Manufacturers Assistance by faxing a request to 301-443-8818 and addressing it to "Publications"
Guidance on IDE policies and procedures (this includes discussions of emergency use of unapproved medical devices and compassionate use of investigational devices): http://www.fda.gov/cdrh/ode/idepolcy.html
Guidance on the review of investigational device exemptions (IDE) applications for feasibility studies, IDE Guidance Memorandum No. #D89-1, 5/17/89: http://www.fda.gov/cdrh/d891.html
Device Advice, a self-service site for information on device regulation: http://www.fda.gov/cdrh/devadvice/
Phone listings for review divisions in the Office of Device Evaluation: http://www.fda.gov/cdrh/organiz.html#ODE
Division of Small Manufacturers Assistance: http://www.fda.gov/cdrh/dsma/dsmamain.html FDA/CDRH/OHIP/DSMA (HFZ-220), 1350 Piccard Dr, Rockville, MD 20850-4307; phone 800-638-2041; fax: 301-443-8818; dsma@cdrh.fda.gov.
Although the current Internet addresses for these sources of information are provided, the same information may be obtained from the Division of Small Manufacturers Assistance.

questions of effectiveness, such as whether the devices adequately exclude the aneurysms, maintain adequate blood flow, and prevent or reduce the risk of rupture. Evaluation of the devices after implantation requires the development of a rational follow-up protocol that includes clinical evaluation and imaging studies to document effectiveness and to detect clinical events, such as persistent blood flow into the aneurysm or aneurysm enlargement. In the case of endovascular grafts, the clinical importance and incidence of adverse sequela related to persistent perigraft leaks or retrograde flow from collateral vessels is unclear. The regulatory approach to these issues may change as both the technology and the understanding of the devices by the clinical community and the FDA evolve.

THE INDIVIDUAL SPONSOR-INVESTIGATOR

Although the development of an IDE application may seem a daunting proposition for a sponsor-investigator, interactions with the FDA and the use of available resources make this task practicable (Table II). The FDA recognizes that individual investigators may not have the same goals in conducting clinical studies as do manufacturers. As such, studies may be designed differently by sponsor-investigators as compared with manufacturers. If so, the reports of prior investigations may also differ from those in IDE applications sponsored by manufacturers. However, adequate information to justify the use of the device in the proposed patient population must be provided, regardless of the nature of the sponsor or the study. The pre–IDE approval process may be particularly helpful to the sponsor-investigator in providing feedback on a "draft IDE application," particularly because sponsor-investigators generally have less experience than manufacturers in the preparation of IDE applications.

Research conducted in accordance with the IDE regulation benefits the public health because the FDA acts as a repository for information on device development and clinical investigations. The sharing of information directly with the FDA enhances the knowledge of FDA personnel regarding devices currently under development. Although the FDA maintains strict confidentiality regarding IDE applications and the results of the clinical investigations, the knowledge gained assists the FDA in its review of related devices and may affect the FDA's requirements for and interactions with other sponsors or manufacturers. For example, difficulties encountered by a clinician in using a device in a particular patient population may lead to the FDA recommending that other sponsors address or consider restricting the use of their device in those patients. The FDA also may take steps to ensure that the labeling for the device specifically addresses the use of the device for those patients.

Many clinicians are frustrated that devices may be available abroad before approval is received for marketing in the United States. The individual investigator can be proactive in addressing the issue of availability of devices in the United States by understanding the system and by actively participating in the design and conduct of clinical investigations. This will help to ensure that scientifically valid information is provided to the FDA in support of marketing applications.

Endovascular grafts: an example. As a simplified hypothetical example, consider a proposed investigation in which abdominal aortic aneurysms would be treated with an endovascular graft constructed with legally marketed devices—ie, stents and vascular graft materials. The principal investiga-

tor learned the technique during a fellowship with a leader in the specialty and wanted to offer this treatment option to patients who are not surgical candidates. The investigator prepared a protocol for review by the IRB. The IRB determined that FDA approval would be required, but it did approve the study subject to FDA review. The investigator contacted one of the FDA reviewers who handles these types of devices for assistance in drafting the IDE application. The reviewer, in addition to providing verbal advice during their conversation, forwarded a package of information to the investigator.

The investigator's major task in the preparation of an IDE application was the development of the report of prior investigations—the section that provided the justification for the study. This section required the most additional effort beyond that which was already required for the application prepared for IRB review. The investigator approached the development of this section by considering such questions as: are the device or the components of the device legally marketed in the United States for any intended use; how will the marketed device be modified for use in the study; what concerns need to be addressed as a result of the modifications; does the new intended use raise additional concerns as compared with the labeled intended use; what are the alternative treatment options for the patients defined by the selection criteria in the protocol; how long is the device intended to function or be used; and is information available from the published literature, the manufacturer, or personal experience to address all concerns and support the assumption that the benefits to the defined patient population should outweigh the risks?

In this example of the endovascular graft, the following points were considered in drafting the report of prior investigations:

1. The device was to be constructed by combining legally marketed devices, each of which was indicated for use in the vascular system. Thus, there were no biocompatibility issues because those issues would have been addressed as part of the marketing applications for the devices.
2. The devices were to be modified by sewing them together, followed by resterilization in accordance with the labeling for both devices. The sewing of the devices together raised the question as to whether the devices would stay together during the manipulations required for implantation and over time. There were no new concerns related to the sterilization of the device because this was to be performed in accordance with the device labeling for both devices.
3. The new intended use required the anchoring of the prosthesis in place intraluminally. This raised questions, such as whether the device would migrate, erode through the vessel wall, fail as a result of fatigue, and adequately exclude the aneurysm.
4. The protocol was designed to include only patients who presented a high surgical risk. Thus, the selection criteria were adequately defined to exclude all patients who could have been treated with standard surgical repair. Given that the patients did not have a viable treatment option, the risks associated with the endovascular repair were compared with the risk of aneurysm rupture rather than the risk of standard surgical therapy.
5. The device was intended to function for the life of the patient. To define the life of the patient, the investigator considered what the expected life of the patient population would have been without treatment. The fact that this was a "high-risk" population allowed for the consideration of a shorter time frame, perhaps 2 years rather than 10 to 30 years for good surgical candidates.

The investigator identified the appropriate published literature, information from the manufacturers of the component devices, and personal experience to address these issues and to confirm the assumption that the benefits to the patients would outweigh the risks. Fortunately for the investigator and the potential patients, this could be accomplished with little or no additional preclinical testing because the experience of the mentor, the personal experience of the investigator, the available information on the legally marketed device components, and other information available in the literature allowed the investigator to adequately address all concerns to justify the initiation of a feasibility study in this limited patient population. In the future, if the investigator proposed treating patients at lower risk, additional information would be needed to address the different balance between the risks and benefits and to show that the device would be expected to function for the same duration as a standard surgical repair. Some of that information would be collected during this feasibility study in the patients at high risk.

The investigator prepared a draft of the IDE application that included the completed report of prior investigations, the clinical protocol previously presented to the IRB, and the additional information delineated in the IDE Manual. This draft was identified as a pre-IDE application and mailed to the IDE Document Mail Center to the attention of the

reviewer previously contacted. The reviewer read the document and provided suggestions for revisions to the investigator by facsimile within 60 days. The sponsor-investigator made the suggested changes, submitted the official IDE application, and within 30 days received approval to begin the investigation. The IRB also had approved the final clinical protocol, and the study commenced. The sponsor conducted the investigation in accordance with the IDE regulation. By gaining FDA approval of the investigation, the IRB remained in conformance with its responsibilities and allowed for potential reimbursement through the HCFA for the devices, even though they are not used in accordance with their approved labeling.

SUMMARY

The purpose of the IDE regulation is to encourage the discovery and the development of useful devices, intended for human use, to the extent consistent with the protection of public health and safety and with ethical standards. Investigators should be aware of the distinctions between significant and nonsignificant risk studies and between clinical investigations and practice of medicine. The FDA can assist in the development of a device and the investigational plan whether the sponsor is a manufacturer or an individual investigator. The FDA encourages active participation by clinicians in the development and regulation of medical devices as part of the collaborative effort required both for medical innovation and for the dissemination of new products to the broader market.

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13. 21 CFR Sect 812.25.
14. 21 CFR Sect 812, subpart B.
15. 61 FR 48417-48425 (1995).
16. 42 CFR Sect 405, subpart B.